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Date: February 18, 2000

Docket No.: 2801-136P

Assistant Commissioner for Patents Washington, DC 20231

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Sir:

This is a Request for filing a  $\boxtimes$  continuation  $\square$  divisional application under 37 C.F.R.  $\S$  1.53(b) of pending prior Application No. 08/945,141 filed on October 14, 1997, the entire contents of which are hereby incorporated by reference, by

Ignatius Loy Britto

for

METERED DOSE INHALER FOR BECLOMETHASONE DIPROPIONATE

- Enclosed is an application consisting of specification, claims, declaration and drawings/photographs (if applicable).
- 2.  $\square$  The filing fee has been calculated as follows:

Docket No. 2801-136P Continuation of Appln. No.: 08/945,141

			LARGE	ENTITY	SMALL	ENTITY
	BASIC FEE		\$690.00		\$345.00	
_	NUMBER FILED	NUMBER EXTRA	RATE	FEE	RATE	FEE
TOTAL CLAIMS	30-20 =	10	x 18 =	\$180.00	x 9 =	\$0.00
INDEPENDENT CLAIMS	2-3 =	0	x 78 =	\$0.00	х 39 =	\$0.00
☐ MULTIPLE DEPENDENT CLAIMS PRESENTED			+ \$2	60.00	+ \$1	30.00
		TOTAL	\$87	0.00	\$0	.00

- 3.  $\sqrt{\boxtimes}$  A check in the amount of \$870.00 to cover the filing fee and recording fee (if applicable) is enclosed.
- 4. Please charge Deposit Account No. 02-2448 in the amount of \$0.00. A triplicate copy of this request is enclosed.
- 5. Amend the specification by inserting before the first line thereof the following:
  - a. \_ --This application is a \_ continuation \_ divisional of co-pending Application No. 08/945,141, filed on, the entire contents of which are hereby incorporated by reference.--
- 6. Transfer the drawings/photographs from the prior application to this application and abandon said prior application as of the filing date accorded this application. A duplicate copy of this request is enclosed for filing in the prior application file.

7.		Enclosed is/are () sheet(s) of drawings and/or photographs.
8.		A statement claiming small entity status was filed in prior Application No. 08/945,141 on See the attached copy of the statement claiming small entity status.
9.	$\boxtimes$	The prior application is assigned to <a href="GlaxoWellcome">GlaxoWellcome</a> , <a href="Inc.">Inc.</a>
10.	/⊠	A Preliminary Amendment is enclosed.
11a.		Priority of Application No(s). filed in on is/are claimed under 35 U.S.C. § 119. See attached copy of the Letter claiming priority filed in the prior application on
11b.		Priority of International Appln. filed on under the Patent Cooperation Treaty and Application No. filed in on under 35 U.S.C. § 119 and/or 35 U.S.C. § 120 are hereby reclaimed.
12.	/⊠	An Information Disclosure Statement and PTO-1449 form(s) are attached hereto for the Examiner's consideration.
13.	$\boxtimes$	Address all future communications to:
		BIRCH, STEWART, KOLASCH & BIRCH, LLP P.O. Box 747 Falls Church, VA 22040-0747 Telephone: (703) 205-8000 or Customer No. 2292
14.		An extension of time for() month(s) until has been submitted in parent Application No. 08/945,141 in order to establish co-pendency with the present application.
15.		Also enclosed herewith is the following:

Docket No. 2801-136P Continuation of Appln. No.: 08/945,141

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

d M. Murphy, Jr., #28,97

P.O. Box

Falls Church VA 22040-0747 (703) 205-8000

GMM/MWM/las/cc 2801-136P

Attachments:

Check in the amount of \$852.00

Preliminary Amendment

Specification

Information Disclosure Statement & PTO Form-1449

Copy of Executed Declaration

(Rev. 01/08/2000)

Docket No. 2801-136P

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS:

Ignatius Loy BRITTO

APPLN. NO.:

NEW

GROUP:

Unassigned

FILED:

February 18, 2000

EXAMINER: Unassigned

FOR:

METERED DOSE INHALER FOR BECLOMETHASONE DIPROPIONATE

#### PRELIMINARY AMENDMENT

Assistant Commissioner of Patents Washington, DC 20231

February 18, 2000

Sir:

The following preliminary amendments and remarks are respectfully submitted in connection with the above-identified application.

#### In the Specification:

Please amend the specification as follows.

#### Page 1

On the first line of the specification, after the title, insert --This application is a 37 C.F.R. § 1.53(b) continuation of copending U.S. Application No. 08/945,141, which was filed pursuant to 35 U.S.C. § 371 as a United States National Phase Application of International Application No. PCT/US96/05009 filed April 11, 1996, which claims priority from U.S. Application 08/422,280, filed April 14, 1995, abandoned. The entire contents of each of the above-identified applications are hereby incorporated by reference.--

#### Page 5

Line 10, change "valve then" to --valve. Then--

#### Page 6

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Line 18, change "(PTFE)" to --(TFE; which is used to prepare polytetrafluoroethylene (PTFE))--; change "fluorinated" to --perfluorinated--; change "(FEP)" to --(FEP; which is perfluorinated ethylene propylene copolymer, which is a copolymer of TFE and hexafluoropropylene (HFP))--

Line 19, change "perfluoroalkoxyalkane (PFA)" to

--perfluoroalkoxyalkylene (PFA; which is a perfluoroalkoxy

fluorocarbon polymer which is prepared using a perfluoroalkyl vinyl

ether monomer) --; change "(ETFE)" to --(ETFE; ethylene
tetrafluoroethylene copolymer) --

Line 20, change "vinyldienefluoride (PVDF)" to --vinylidene fluoride (PVDF; polyvinylidene fluoride)--; and after "chlorinated ethylene tetrafluoroethylene" insert -- (a copolymer made by copolymerizing chlorinated ethylene and tetrafluoroethylene)--

#### Page 7

Line 2, after "Hostaflon®" insert -- (a copolymer prepared by copolymerizing TFE and perfluoropropyl vinyl ether)--

Line 3, after "PFA DuPont 857-200" insert --(a copolymer prepared by copolymerizing TFE and perfluoropropyl vinyl ether)-Page 8

Line 27, change "proper" to --primer--

#### In the Claims:

Please cancel claims 1-21 without prejudice or disclaimer to the subject matter contained therein.

Please add the following claims.

--22. A metered dose inhaler ("MDI"), comprising:

a can having part or all of its internal surfaces coated with a polymer blend comprising one or more fluorocarbon polymers, in combination with one or more non-fluorocarbon polymers;

- a crimped cap covering the mouth of the can; and
- a drug metering valve situated on the cap. --

- --23. The MDI according to claim 22, further comprising an inhalation medicament formulation, comprising a medicament formulated with a fluorocarbon propellant.--
- --24. The MDI according to claim 23, wherein said medicament formulation further comprises a surfactant.--
- --25. The MDI according to claim 23, wherein said medicament formulation further comprises a polar solvent.--
- --26. The MDI according to claim 23, wherein said medicament formulation comprises 0.01 to 5 % w/w based on the weight of propellant of a polar cosolvent.--

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- --27. The MDI according to claim 25, wherein the polar solvent is ethanol.--
- --28. The MDI according to claim 22, further containing a medicament formulated with a fluorocarbon propellant and 0.01 to 5 % w/w based on the propellant of a polar cosolvent, which formulation is substantially free of surfactant.--

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--29. The MDI according to claim 23, wherein the fluorocarbon propellant is 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoro-n-propane or a mixture thereof.--

- --30. The MDI according to claim 29, wherein the fluorocarbon propellant is 1,1,1,2-tetrafluoroethane.--
- --31. The MDI according to claim 22, wherein said can is made of metal and wherein part or all of the internal metallic surfaces are coated.--

- --32. The MDI according to claim 31, wherein the metal is aluminum or an alloy thereof.--
- --33. The MDI according to claim 22, wherein said one or more fluorocarbon polymers is a perfluorocarbon polymer.--
- --34. The MDI according to claim 33, wherein said one or more fluorocarbon polymers is selected from the group consisting of polytetrafluoroethylene, perfluoroalkoxyalkylene, perfluorinated ethylene propylene copolymer and a mixture thereof.--

- --35. The MDI according to claim 22, wherein said one or more fluorocarbon polymers is blended with a non-fluorocarbon polymer selected from the group consisting of polyamideimide and polyethersulfone.--
- --36. The MDI according to claim 22, wherein said comprises a substantially ellipsoidal base.
- --37. The MDI according to claim 22, wherein said fluorocarbon polymer comprises monomeric units made from one or more monomers selected from the group consisting of tetrafluoroethylene, hexafluoropropylene, perfluoroalkoxyalkylene, and vinylidene fluoride.--
- --38. The MDI according to claim 22, wherein said non-fluorinated polymer is selected from the group consisting of a polyamide, a polyamide, a polyamide, a polyamideimide, a polyethersulfone, a polyphenylene sulfide and an amine-formaldehyde thermosetting resin.--
- --39. The MDI according to claim 38, wherein said non-fluorinated polymer is a polyethersulfone.--
- --40. The MDI according to claim 34, wherein said fluorinated polymer is polytetrafluoroethylene.--

- --41. The MDI according to claim 22, wherein said blend comprises polytetrafluoroethylene and polyethersulfone.--
- --42. The MDI according to claim 22, wherein said blend consists of polytetrafluoroethylene and polyethersulfone.--
- --43. The MDI according to claim 22, wherein said fluorinated polymer is made from monomeric units comprising perfluoroalkoxyalkylene.--
- --44. The MDI according to claim 22, wherein said fluorinated polymer is made from monomeric units comprising perfluorinated ethylene propylene.--
- --45. The MDI according to claim 22, wherein the thickness of said coating is 1  $\mu m$  to 1 mm.--
- --46. The MDI according to claim 22, wherein the thickness of said coating is 1  $\mu m$  to 100  $\mu m.--$
- --47. The MDI according to claim 22, wherein the thickness of said coating is 1  $\mu m$  to 25  $\mu m.--$

- --48. The MDI according to claim 31, wherein said coating is applied to said internal surface of a preformed can.--
- --49. The MDI according to claim 31, wherein said coating is applied by spray coating said polymer blend.--
- --50. The MDI according to claim 31, wherein said coating is applied by spray coating said polymer blend on the internal metallic surface of said can and curing said coating after it is sprayed.--
- --51. A metered dose inhaler can, comprising:

a metered dose inhaler can having part or all of its internal surfaces coated with a polymer blend comprising one or more fluorocarbon polymers, in combination with one or more non-fluorocarbon polymers.--

#### REMARKS

The present application has been filed to claim subject matter disclosed in the parent application but not specifically covered by the allowed claims in the parent application. For example, new claim 22 has does not have the language concerning the "intended use" of the metered dose inhaler (MDI), e.g., "for dispensing . . . ."

Dependent claim 23 and other claims which recite that the MDI further contains a medicament and a propellant, cover this feature.

The above amendments to the specification are the same ones made in the parent application. They have been made in order to correct typographical errors on page 6 of the specification, e.g., "vinyldiene" to "vinylidene" and at page 8, line 27. The specification has also been amended to provide definitions for the various abbreviations and to identify the "monomers" and/or "monomeric units" that some of the polymers are made from.

Support for new claim 22 can be found page 6, lines 15-32 and page 7, lines 20-30. Support for new claims 23 and 28 can be found on page 4, lines, 12-33 and page 5, lines 6-14 and page 3, lines 19-24. Support for new claims 37 and 38 can be found on page 6, lines 18-20 and page 6, lines 25-28, respectively. The support for new claims 45-47 can be found on page 7, lines 5-7. The support for new claims 48 and 49 can be found on page 9, lines 7-9. All other new claims are rewritten from the original claims so that dependencies are easier to follow.

If there are any minor matters precluding allowance of the application which may be resolved by a telephone discussion, the Examiner is respectfully requested to contact Mark W. Milstead (Reg. No. P-45,825) at (703) 205-8000.

Attorney Docket No. 2801-136P R53(b) Continuation of Application No.: 08/945,141

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §\$1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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GMM/MWM/las/cc

2801-136P

### METERED DOSE INHALER FOR BECLOMETHASONE DIPROPIONATE

#### **BACKGROUND OF THE INVENTION**

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Drugs for treating respiratory and nasal disorders are frequently administered in aerosol formulations through the mouth or nose. One widely used method for dispensing such aerosol drug formulations involves making a suspension formulation of the drug as a finely divided powder in a liquefied gas known as a propellant. The suspension is stored in a sealed container capable of withstanding the pressure required to maintain the propellant as a liquid. The suspension is dispersed by activation of a dose metering valve affixed to the container.

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A metering valve may be designed to consistently release a fixed, predetermined mass of the drug formulation upon each activation. As the suspension is forced from the container through the dose metering valve by the high vapor pressure of the propellant, the propellant rapidly vaporizes leaving a fast moving cloud of very fine particles of the drug formulation. This cloud of particles is directed into the nose or mouth of the patient by a channelling device such as a cylinder or open ended cone. Concurrently with the activation of the aerosol dose metering valve, the patient inhales the drug particles into the lungs or nasal cavity. Systems of dispensing drugs in this way are known as "metered dose inhalers" (MDI's). See Peter Byron, Respiratory Drug Delivery, CRC Press, Boca Raton, FL (1990) for a general background on this form of therapy.

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Patients often rely on medication delivered by MDI's for rapid treatment of respiratory disorders which are debilitating and in some cases, even life threatening. Therefore, it is essential that the prescribed dose of aerosol medication delivered to the patient consistently meet the specifications claimed by the manufacturer and comply with the requirements of the FDA and other

regulatory authorities. That is, every dose in the can must be the same within close tolerances.

Some aerosol drugs tend to adhere to the inner surfaces, i.e., walls of the can, valves, and caps, of the MDI. This can lead to the patient getting significantly less than the prescribed amount of drug upon each activation of the MDI. The problem is particularly acute with hydrofluoroalkane (also known as simply "fluorocarbon" propellant systems, e.g., P134a and P227, under development in recent years to replace chlorofluorocarbons such as P11, P114, and P12.

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We have found that coating the interior can surfaces of MDI's with a fluorocarbon polymer significantly reduces or essentially eliminates the problem of drug adhesion or deposition on the can walls and thus ensures consistent delivery of medication in aerosol form from the MDI.

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#### **SUMMARY OF THE INVENTION**

A metered dose inhaler having part or all of its internal metallic surfaces coated with one or more fluorocarbon polymers, optionally in combination with one or more non-fluorocarbon polymers, for dispensing an inhalation drug formulation comprising beclomethasone dipropionate or a physiologically acceptable solvate thereof, and a fluorocarbon propellant, optionally in combination with one or more other pharmacologically active agents or one or more excipients.

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#### **DETAILED DESCRIPTION OF THE INVENTION**

The term "metered dose inhaler" or "MDI" means a unit comprising a can, a crimped cap covering the mouth of the can, and a drug metering valve situated in the cap, while the term "MDI system" also includes a suitable channelling device. The terms "MDI can" means the container without the cap and valve. The term "drug metering valve" or "MDI valve" refers to a valve and its associated mechanisms which delivers a predetermined amount of drug formulation from an MDI upon each activation. The channelling device may

comprise, for example, an actuating device for the valve and a cylindrical or cone-like passage through which medicament may be delivered from the filled MDI can via the MDI valve to the nose or mouth of a patient, e.g. a mouthpiece actuator. The relation of the parts of a typical MDI is illustrated in US Patent 5,261,538 incorporated herein by reference.

U.S. Patent No.3,312,590, incorporated herein by reference, teaches an antiinflammatory steroid compound know by the chemical name 9-chloro-1 1D, 17, 21-trihydroxy-16fi-methylprergna-1,4-diene-3, 20-dione 17, 21-dipropionate and the generic name "beclomethasone dipropionate". Beclomethasone dipropionate in aerosol form, has been accepted by the medical community as useful in the treatment of asthma and is marketed under the trademarks "Beclovent", "Becotide", and "Beconase".

The term "drug formulation" means beclomethasone dipropionate (or a physiologically acceptable solvate thereof) optionally in combination with one or more other pharmacologically active agents such as other antiinflammatory agents, analgesic agents or other respiratory drugs and optionally containing one or more excipients. The term "excipients" as used herein mean chemical agents having little or no pharmacological activity (for the quantities used) but which enhance the drug formulation or the performance of the MDI system. For example, excipients include but are not limited to surfactants, preservatives, flavorings, antioxidants, antiaggregating agents, and cosolvents, e.g., ethanol and diethyl ether.

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Suitable surfactants are generally known in the art, for example, those surfactants disclosed in European Patent Application No. 0327777. The amount of surfactant employed is desirable in the range of 0.0001% to 50% weight to weight ratio relative to the drug, in particular, 0.05 to 5% weight to weight ratio. A particularly useful- surfactant is 1,2-di[7-(F-hexyl) hexanoyl]-glycero-3-phospho-N,N,N-trimethylethanolamine also know as 3, 5, 9-trioxa-4-phosphadocosan-1-aminium, 17, 17, 18,18,19, 19, 20, 20, 21, 21, 22, 22, 22-tridecafluoro-7-[(8, 8, 9, 9,10, 10, 11, 11, 12, 12, 13, 13, 13-tridecafluoro-1-oxotridecyl)oxy]-4-hydroxy-N, N, N-trimethyl-10-oxo-, inner salt, 4-oxide.

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A polar cosolvent such as  $C_{2-6}$  aliphatic alcohols and polyols eg ethanol, isopropanol and propylene glycol, and preferably ethanol, may be included in the drug formulation in the desired amount, either as the only excipient or in addition to other excipients such as surfactants. Suitably, the drug formulation may contain 0.01 to 5% w/w based on the propellant of a polar cosolvent eg ethanol, preferably 0.1 to 5% w/w e.g. 0.1 to 1% w/w.

It will be appreciated by those skilled in the art that the drug formulation for use in the invention may, if desired, contain beclomethasone dipropionate (or a physiologically acceptable solvate thereof) in combination with one or more other pharmacologically active agents. Such medicaments may be selected from any suitable drug useful in inhalation therapy. Appropriate medicaments may thus be selected from, for example, analgesics, e.g. codeine, dihydromorphine, ergotamine, fentanyl or morphine; anginal preparations, e.g. diltiazem; antiallergics, e.g. cromoglycate, ketotifen or nedocromil; antiinfectives e.g. cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines and pentamidine; antihistamines, e.g. methapyrilene; anti-inflammatories, e.g. fluticasone (e.g. the propionate), flunisolide, budesonide, tipredane or triamcinolone acetonide; antitussives, e.g. noscapine; bronchodilators, e.g. salbutamol, salmeterol, ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimiterol, terbutaline, isoetharine, tulobuterol, orciprenaline, or (-)-4-amino-3,5dichloro- $\alpha$  -[[[6-[2-(2-pyridinyl)ethoxy]hexyl]amino]methyl]benzenemethanol; diuretics, e.g. amiloride; anticholinergics e.g. ipratropium, atropine or oxitropium; hormones, e.g. cortisone, hydrocortisone or prednisolone; xanthines e.g. aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; and therapeutic proteins and peptides, e.g. insulin or glucagon. It will be clear to a person skilled in the art that, where appropriate, the medicaments may be used in the form of salts (e.g. as alkali metal or amine salts or as acid addition salts) or as esters (e.g. lower alkyl esters) or as solvates (e.g. hydrates) to optimise the activity and/or stability of the medicament and/or to minimise the solubility of the medicament in the propellant.

Particularly preferred drug formulations contain beclomethasone dipropionate (or a physiologically acceptable solvate thereof) in combination with a bronchodilator such as salbutamol (e.g. as the free base or the sulphate salt) or salmeterol (e.g. as the xinafoate salt).

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"Propellants" used herein mean pharmacologically inert liquids with boiling points from about room temperature (25°C) to about -25°C which singly or in combination exert a high vapor pressure at room temperature. Upon activation of the MDI system, the high vapor pressure of the propellant in the MDI forces a metered amount of drug formulation out through the metering valve then the propellant very rapidly vaporizes dispersing the drug particles. The propellants used in the present invention are low boiling fluorocarbons; in particular, 1,1,1,2-tetrafluoroethane also known as "propellant 134a" or "P134a" and 1,1,1,2,3,3,3-heptafluoropropane also known as "propellant 227" or "P 227".

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Drug formulations for use in the invention may be free or substantially free of formulation excipients e.g. surfactants and cosolvents etc. Such drug formulations are advantageous since they may be substantially taste and odour free, less irritant and less toxic than excipient-containing formulations. Thus, a preferred drug formulation consists essentially of beclomethasone dipropionate (or a physiologically acceptable solvate thereof), optionally in combination with one or more other pharmacologically active agents particularly salbutamol (or a physiologically acceptable salt thereof), and a fluorocarbon propellant. Preferred propellants are 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or mixtures thereof, and especially 1,1,1,2-tetrafluoroethane.

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Most often the MDI can and cap are made of aluminum or an alloy of aluminum, although other metals not affected by the drug formulation, such as stainless steel, an alloy of copper, or tin plate, may be used. An MDI can may also be fabricated from glass or plastic. Preferably, however, the MDI cans employed in the present invention are made of aluminium or an alloy thereof. Advantageously, strengthened aluminium or aluminum alloy MDI cans may be employed. Such strengthened MDI cans are capable of withstanding particularly stressful coating and curing conditions, e.g. particularly high temperatures, which

may be required for certain fluorocarbon polymers. Strengthened MDI cans which have a reduced tendency to malform under high temperatures include MDI cans comprising side walls and a base of increased thickness and MDI cans comprising a substantially ellipsoidal base (which increases the angle between the side walls and the base of the can), rather than the hemispherical base of standard MDI cans. MDI cans having an ellipsoidal base offer the further advantage of facilitating the coating process.

The drug metering valve consists of parts usually made of stainless steel, a pharmacologically inert and propellant resistant polymer, such as acetal, polyamide (e.g., Nylon®), polycarbonate, polyester, fluorocarbon polymer (e.g., Teflon®) or a combination of these materials. Additionally, seals and "O" rings of various materials (e.g., nitrile rubbers, polyurethane, acetyl resin, fluorocarbon polymers), or other elastomeric materials are employed in and around the valve.

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Fluorocarbon polymers for use in the invention include fluorocarbon polymers which are made of multiples of one or more of the following monomeric units: tetrafluoroethylene (PTFE), fluorinated ethylene propylene (FEP), perfluoroalkoxyalkane (PFA), ethylene tetrafluoroethylene (ETFE), vinyldienefluoride (PVDF), and chlorinated ethylene tetrafluoroethylene. Fluorinated polymers which have a relatively high ratio of fluorine to carbon, such as perfluorocarbon polymers e.g. PTFE, PFA, and FEP, are preferred.

The fluorinated polymer may be blended with non-fluorinated polymers such as polyamides, polyimides, polyethersulfones, polyphenylene sulfides and amine-formaldehyde thermosetting resins. These added polymers improve adhesion of the polymer coating to the can walls. Preferred polymer blends are PTFE/FEP/polyamideimide, PTFE/polyethersulphone (PES) and FEP-benzoguanamine.

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Particularly preferred coatings are pure PFA, FEP and blends of PTFE and polyethersulphone (PES).

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Fluorocarbon polymers are marketed under trademarks such as Teflon®, Tefzel®, Halar®, Hostaflon®, Polyflon® and Neoflon®. Grades of polymer include FEP DuPont 856-200, PFA DuPont 857-200, PTFE-PES DuPont 3200-100, PTFE-FEP-polyamideimide DuPont 856P23485, FEP powder DuPont 532 and PFA Hoechst 6900n. The coating thickness is in the range of about 1μm to about 1mm. Suitably the coating thickness is in the range of about 1μm to about 100μm, e.g. 1μm to 25μm. Coatings may be applied in one or more coats.

Preferably the fluorocarbon polymers for use in the invention are coated onto MDI cans made of metal, especially MDI cans made of aluminium or an alloy thereof.

The particle size of the particular (e.g., micronised) drug should be such as to permit inhalation of substantially all the drug into the lungs upon administration of the aerosol formulation and will thus be less than 100 microns, desirably less than microns, and, in particular, in the range of 1-10 microns, e.g., 1-5 microns.

The final aerosol formulation desirably contains 0.005-10% weight to weight ratio, in particular 0.005-5% weight to weight ratio, especially 0.01-1.0% weight to weight ratio, of drug relative to the total weight of the formulation.

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A further aspect of the present invention is a metered dose inhaler having part or all of its internal metallic surfaces coated with one or more fluorocarbon polymers, optionally in combination with one or more fluorocarbon polymers, for dispersing an inhalation drug formulation comprising becomethasone dipropionate and a fluorocarbon propellant optionally in combination with one or more other pharmacologically active agents and one or more excipients.

A particular formulation for use in the metered dose inhaler of the present invention comprises:

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- (a) beclomethasone dipropionate monohydrate, the particle size of substantially all the monohydrate being less than 20 microns;
- (b) at least 0.015% by weight of the formulation of water in addition to the water of crystallization associated with said monohydrate; and
- (c) a fluorocarbon propellant.

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Such aerosol formulations desirably contain at least 0.015% (e.g., 0.015 to 0.1%) by weight of the formulation of water (excluding the water of crystallization associated with the beclomethasone dipropionate monohydrate), preferably at least 0.02%, for example 0.025% by weight or more of added water. Preferred formulations according to the invention contain at least 0.026%, for example 0.026 to 0.08% by weight of water, in addition to the water of crystallization associated with the beclomethasone dipropionate monohydrate. Optionally, a cosolvent such as ethanol may be included in the formulation in the desired amount. Suitably, the formulation may contain 0.05 to 3.0% w/w based on the propellant of a polar cosolvent such as ethanol. Preferably the fluorocarbon propellant is 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or mixtures thereof, and especially 1,1,1,2-tetrafluoroethane.

Further drug formulations for use in the invention are free or substantially free of surfactants. Thus, a further formulation comprises or consists essentially of beclomethasone dipropionate or a physiologically acceptable solvate thereof, optionally in combination with one or more other pharmacologically active agents, a fluorocarbon propellant and 0.01 to 0.05% w/w based on the propellant of a polar cosolvent such as ethanol, which formulation is free of surfactant. Preferably the propellant is 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoro-n-propane, although mixtures thereof may also be used.

A particular aspect of the present invention is an MDI having part or essentially all of its internal surfaces e.g. metallic surfaces coated with PFA or FEP, or blended fluoropolymer resin systems such as PTFE-PES with or without a proper coat of polyamideimide or polyethersulfone for dispersing a drug formulation as defined hereinabove. Preferably the MDI can is made of aluminum or an alloy thereof.

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The MDI can may be coated by the means known in the art of metal coating. For example, a metal, such as aluminum or stainless steel, may be precoated as coil stock and cured before being stamped or drawn into the can shape. This method is well is suited to high volume production for two reasons. First, the art of

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Other techniques for obtaining coated cans is by electrostatic dry powder coating or by spraying preformed MDI cans inside with formulations of the coating fluorinated polymer/polymer blend and then curing. The preformed MDI cans may also be dipped in the fluorocarbon polymer/polymer blend coating formulation and cured, thus becoming coated on the inside and out. The fluorocarbon polymer/polymer blend formulation may also be poured inside the MDI cans then drained out leaving the insides with the polymer coat. Conveniently, for ease of manufacture, preformed MDI cans are spray-coated with the fluorinated polymer/polymer blend.

The fluorocarbon polymer/polymer blend may also be formed in situ at the can walls using plasma polymerization of the fluorocarbon monomers. Fluorocarbon polymer film may be blown inside the MDI cans to form bags. A variety of fluorocarbon polymers such as ETFE, FEP, and PTFE are available as film stock.

The appropriate curing temperature is dependent on the fluorocarbon polymer/polymer blend chosen for the coating and the coating method employed. However, for coil coating and spray coating temperatures in excess of the melting point of the polymer are typically required, for example, about 50° C above the melting point for up to about 20 minutes such as about 5 to 10 minutes eg about 8 minutes or as required. For the above named preferred and particularly preferred fluorocarbon polymer/polymer blends curing temperatures in the range of about 300°C to about 400°C, e.g. about 350°C to 380°C are suitable. For plasma polymerization typically temperatures in the range of about 20°C to about 100°C may be employed.

The fluorocarbon polymer may also be formed in situ at the can walls using plasma polymerization of the fluorocarbon monomers. Fluorocarbon polymer film

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The MDI's taught herein may be prepared by methods of the art (e.g., see Byron, above and U.S. patent 5,345,980) substituting conventional cans for those coated with a fluorinated polymer. That is, beclomethasone dipropionate and other components of the formulation are filled into an aerosol can coated with a fluorinated polymer. The can is fitted with a cap assembly which is crimped in place. The suspension of the drug in the fluorocarbon propellant in liquid form may be introduced through the metering valve as taught in U.S. 5,345,980 incorporated herein by reference.

The MDI's with fluorocarbon coated interiors taught herein may be used in medical practice in a similar manner as non-coated MDI's now in clinical use.

However the MDI's taught herein are particularly useful for containing and dispensing inhaled drug formulations with hydrofluoroalkane fluorocarbon propellants such as 134a with little, or essentially no, excipient and which tend to deposit or cling to the interior walls and parts of the MDI system. In certain case it is advantageous to dispense an inhalation drug with essentially no excipient, e.g., where the patient may be allergic to an excipient or the drug reacts with an excipient.

MDI's containing the formulations described hereinabove, MDI systems and the use of such MDI systems for the treatment of respiratory disorders e.g. asthma comprise further aspects of the present invention.

It will be apparent to those skilled in the art that modifications to the invention described herein can readily be made without departing from the spirit of the invention. Protection is sought for all the subject matter described herein including any such modifications.

The following non-limitative Examples serve to illustrate the invention.

#### **EXAMPLES**

#### Example 1

Standard 12.5 mL MDI cans (Presspart Inc., Cary, NC) were spray-coated (Livingstone Coatings, Charlotte, NC) with primer (DuPont 851-204) and cured to the vendor's standard procedure, then further spray-coated with either FEP or PFA (DuPont 856-200 and 857-200, respectively) and cured according to the vendor's standard procedure. The thickness of the coating is approximately 10μm to 50μm. These cans are then purged of air (see PCT application number W094/22722 (PCT/EP94/00921)), the valves crimped in place, and a suspension of about 24 mg beclomethasone dipropionate in about 18 gm P134a is filled through the valve.

15 <u>Example 2</u>

Standard 0.46 mm thick aluminum sheet (United Aluminum) was spray-coated (DuPont, Wilmington, DE) with FEP (DuPont 856-200) and cured. This sheet was then deep-drawn into cans (Presspart Inc., Cary, NC). The thickness of the coating is approximately 10µm to 50µm. These cans are then purged of air, the valves crimped in place, and a suspension of about 60 mg beclomethasone dipropionate in about 18 gm P134A is filled through the valve.

#### Example 3

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Standard 12.5 ml MDI cans (Presspart Inc., Cary NC) are spray-coated with PTFE-PES blend (DuPont) as a single coat and cured according to the vendor's standard procedure. The thickness of the coating is between approximately 1µm and approximately 20µm. These cans are then purged of air, the valves crimped in place, and a suspension of about 68mg micronised beclomethasone dipropionate monohydrate in about 6.1mg water and about 18.2g P134a is filled through the valve.

#### Example 4

Standard 12.5ml MDI cans (Presspart Inc., Cary NC) are spray-coated with PTFE-FEP-polyamideimide blend (DuPont) and cured according to the vendor's standard procedure. The thickness of the coating is between approximately  $1\mu$ m and approximately  $20\mu$ m. These cans are then purged of air the valves crimped in place, and a suspension of about 68mg micronised beclomethasone dipropionate monohydrate in about 6.1mg water and about 18.2g P134a is filled through the valve.

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#### Example 5

15 Standard 12.5ml MDI cans (Presspart Inc., Cary NC) are spray-coated with FEP powder (DuPont FEP 532) using an electrostatic gun. The thickness of the coating is between approximately 1μm and approximately 20μm. These cans are then purged of air, the valves crimped in place, and a suspension of about 68mg micronised beclomethasone dipropionate monohydrate in about 6.1mg water and about 18.2g P134a is filled through the valve.

#### Example 6

Standard 0.46mm thick aluminium sheet is spray coated with FEP-Benzoguanamine and cured. This sheet is then deep-drawn into cans. These cans are then purged of air, the valves crimped in place, and a suspension of about 68mg micronised beclomethasone dipropionate monohydrate in about 6.1mg water and about 18.2g P134a is filled through the valve.

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#### Example 7

Standard 12.5 ml MDI cans (Presspart Inc., Cary NC) are spray-coated with an aqueous dispersion of PFA (Hoechst PFA-6900n) and cured. The thickness of the coating is between approximately 1µm and approximately 20µm. These cans

are then purged of air, the valves crimped in place, and a suspension of about 68mg micronised beclomethasone dipropionate monohydrate in about 6.1mg water and about 18.2g P134a is filled through the valve.

5 <u>Example 8</u>

Standard 12.5 ml MDI cans (Presspart Inc., Cary NC) are spray-coated with PTFE-PES blend (DuPont) as a single coat and cured according to the vendor's standard procedure. The thickness of the coating is between approximately  $1\mu$ m and approximately  $20\mu$ m. These cans are then purged of air, the valves crimped in place, and about 68mg micronised beclomethasone dipropionate monohydrate in about 182mg ethanol and about 18.2g P134a is filled through the valve.

#### Example 9

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Standard 12.5ml MDI cans (Presspart Inc., Cary NC) are spray-coated with PTFE-FEP-polyamideimide blend (DuPont) and cured according to the vendor's standard procedure. The thickness of the coating is between approximately  $1\mu m$  and approximately  $20\mu m$ . These cans are then purged of air the valves crimped in place, and about 68mg micronised beclomethasone dipropionate monohydrate in about 182mg ethanol and about 18.2g P134a is filled through the valve.

#### Example 10

Standard 12.5ml MDI cans (Presspart Inc., Cary NC) are spray-coated with FEP powder (DuPont FEP 532) using an electrostatic gun. The thickness of the coating is between approximately 1μm and approximately 20μm. These cans are then purged of air, the valves crimped in place, and about 68mg micronised beclomethasone dipropionate monohydrate in about 182mg ethanol and about 18.2g P134a is filled through the valve.

#### Example 11

Standard 0.46mm thick aluminium sheet is spray coated with FEP-Benzoguanamine and cured. This sheet is then deep-drawn into cans. These cans are then purged of air, the valves crimped in place, and about 68mg micronised beclomethasone dipropionate monohydrate in about 182mg ethanol and about 18.2g P134a is filled through the valve.

#### Example 12

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Standard 12.5 ml MDI cans (Presspart Inc., Cary NC) are spray-coated with an aqueous dispersion of PFA (Hoechst PFA-6900n) and cured. The thickness of the coating is between approximately  $1\mu$ m and approximately  $20\mu$ m. These cans are then purged of air, the valves crimped in place, and about 68mg micronised beclomethasone dipropionate monohydrate in about 182mg ethanol and about 18.2g P134a is filled through the valve.

#### Example 13

Standard 12.5 ml MDI cans (Presspart Inc., Cary NC) are spray-coated with PTFE-PES blend (DuPont) as a single coat and cured according to the vendor's standard procedure. The thickness of the coating is between approximately 1μm and approximately 20μm. These cans are then purged of air, the valves crimped in place, and about 13.6mg micronised beclomethasone dipropionate in about 107mg ethanol and about 21.4g P227 is filled through the valve.

#### Example 14

Standard 12.5ml MDI cans (Presspart Inc., Cary NC) are spray-coated with PTFE-FEP-polyamideimide blend (DuPont) and cured according to the vendor's standard procedure. The thickness of the coating is between approximately 1µm and approximately 20µm. These cans are then purged of air the valves crimped in place, and about 13.6mg micronised beclomethasone dipropionate in about 107mg ethanol and about 21.4g P227 is filled through the valve.

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#### Example 15

Standard 12.5ml MDl cans (Presspart Inc., Cary NC) are spray-coated with FEP powder (DuPont FEP 532) using an electrostatic gun. The thickness of the coating is between approximately 1µm and approximately 20µm. These cans are then purged of air, the valves crimped in place, and about 13.6mg micronised beclomethasone dipropionate in about 107mg ethanol and about 21.4g P227 is filled through the valve.

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#### Example 16

Standard 0.46mm thick aluminium sheet is spray coated with FEP-Benzoguanamine and cured. This sheet is then deep-drawn into cans. These cans are then purged of air, the valves crimped in place, and about 13.6mg micronised beclomethasone dipropionate in about 107mg ethanol and about 21.4g P227 is filled through the valve.

#### Example 17

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Standard 12.5 ml MDI cans (Presspart Inc., Cary NC) are spray-coated with an aqueous dispersion of PFA (Hoechst PFA-6900n) and cured. The thickness of the coating is between approximately 1 $\mu$ m and approximately 20 $\mu$ m. These cans are then purged of air, the valves crimped in place, and about 13.6mg micronised beclomethasone dipropionate in about 107mg ethanol and about 21.4g P227 is filled through the valve.

#### Examples 18-22

Examples 3 to 7 are repeated except that about 24mg salbutamol as the free base or equivalent weight of salt e.g. sulphate with about 12mg becomethasone dipropionate monohydrate in about 364mg ethanol and about 18.2g P134a is filled through the valve.

### Examples 23-42

Examples 3 to 22 are repeated except that modified 12.5ml MDI cans having a substantially ellipsoidal base (Presspart Inc., Cary NC) are used.

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Dose delivery from the MDIs tested under simulated use conditions is found to be constant, compared to control MDIs filled into uncoated cans which exhibit a significant decrease in dose delivered through use.

#### We claim:

- 1. A metered dose Inhaler having part or all of its internal surfaces coated with one or more fluorocarbon polymers, optionally in combination with one or more non-fluorocarbon polymers, for dispensing an inhalation drug formulation comprising beclomethasone dipropionate or a physiologically acceptable solvate thereof, and a fluorocarbon propellant, optionally in combination with one or more other pharmacologically active agents or one or more excipients.
- 10 2. An inhaler according to Claim 1 containing said drug formulation.
  - 3. An inhaler according to Claim 2 wherein said drug formulation further comprises a surfactant.
- 4. An inhaler according to Claim 2 or Claim 3 wherein said drug formulation further comprises a polar cosolvent.
- 5. An inhaler according to claim 2 wherein said drug formulation comprises
  0.01 to 5 % w/w based on the weight of propellant of a polar cosolvent, which
  formulation is substantially free of surfactant.
  - 6. An inhaler according to Claim 4 or Claim 5, wherein the polar cosolvent is ethanol.
- 7. An inhaler according to any one of Claims 2 to 6, wherein said drug formulation comprises becomethasone dipropionate or a physiologically acceptable solvate thereof in combination with salmeterol or salbutamol or a physiologically acceptable salt thereof.
- An inhaler according to Claim 2, wherein said drug formulation comprises
   (a) beclomethasone dipropionate monohydrate, the particle size of substantially all the monohydrate being less than 20 microns;
  - (b) at least 0.15% by weight of the formulation of water in addition to the water of crystallisation associated with the monohydrate; and

- (c) a fluorocarbon propellant.
- 9. An inhaler according to Claim 8, wherein the formulation further comprises 0.05 to 3% w/w based on the propellant of a polar cosolvent.
- 10. An inhaler according to Claim 9, wherein the polar cosolvent is ethanol.
- An inhaler according to Claim 2, wherein said drug formulation consists essentially of beclomethasone dipropionate or a physiologically acceptable solvate thereof, optionally in combination with one or more other pharmacologically active agents, a fluorocarbon propellant and 0.01 to 5 % w/w based on the propellant of a polar cosolvent, which formulation is substantially free of surfactant.
- 12. An inhaler according to any one of Claims 2 to 11, wherein the fluorocarbon propellant is 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoron-propane or mixtures thereof.
- 13. An inhaler according to Claim 12, wherein the fluorocarbon propellant is1,1,1,2-tetrafluoroethane.
  - 14. An inhaler according to any one of claims 1 to 13 comprising a can made of metal wherein part or all of the internal metallic surfaces are coated.
- 25 15. An inhaler according to Claim 14 wherein the metal is aluminium or an alloy thereof.
  - 16. An inhaler according to any one of Claims 1 to 15, wherein said fluorocarbon polymer is a perfluorocarbon polymer.
  - 17. An inhaler according to Claim 16 wherein said fluorocarbon polymer is selected from PTFE, PFA, FEP and mixtures thereof.

18. An inhaler according to any one of Claims 1 to 17, wherein said fluorocarbon polymer is in combination with a non-fluorocarbon polymer selected from polyamideimide and polyethersulphone.

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- 5 19. An inhaler according to any one of Claims 1 to 18 comprising a substantially ellipsoidal base.
  - 20. A metered dose inhaler system comprising a metered dose inhaler according to any one of Claim 1 to 19 fitted into suitable channelling device for oral or nasal inhalation of the drug formulation.
  - 21. Use of a metered dose inhaler system according to Claim 20 for the treatment of respiratory disorders.

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#### **ABSTRACT**

A metered dose inhaler having part or all of its internal surfaces coated with one or more fluorocarbon polymers, optionally in combination with one or more non-fluorocarbon polymers, for dispensing an inhalation drug formulation comprising beclomethasone dipropionate or a physiologically acceptable solvate thereof, and a fluorocarbon propellant, optionally in combination with one or more other pharmacologically active agents or one or more excipients.

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COMBINED DECLARA  (Includes Reference to PCT Intern		APPLICATION AND P	OWER OF A	ORNEY	ATTORNEY'S DOCKET NUMBER GI2180USW
As below	named inventor. I her	eby declare that:			
My residence, pos	t office address and citi	izenship are as stated belo	w next to my na	ime.	
I believe I am the (if plural names ar entitled:	original, first and sole is elisted below) of the s	nventor (if only one name ubject matter which is clai	is listed below) med and for wh	) or an original, firs nich a patent is soug	t and joint inventor tht on the invention
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the specification o	f which (check only on	e item below):			
[ ]is attached here	eto with Preliminary A	mendment.			
September 21, 199	98 and September 28, 1	n Serial No. <u>08/945,141</u> 998 (if applicable) cation Number <u>PCT/US9</u>		ber 14, 1997_and v April 11, 1996	/as amended on
and was ame	nded under PCT Article	e 19 on	(if ap	plicable).	
I hereby state that as amended by any	I have reviewed and ur y amendment specifical	nderstand the contents of the large to the l	he above-identii	fied specification, i	acluding the claims,
Regulations, §1.5	6 and all information w	nation which is material to hich became available bet ntinuation-in-part applicati	ween the filing	defined in Title 37 of the prior applica	, Code of Federal tion and the national
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## COMBINED DECLARATION FOR P. LNT APPLICATION AND POWER OF ATTORNEY (Continued - Includes References to PCT International Applications)

ATTORNEY'S DOCKET NUMBER
GI2180USW

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or §365(c) of any PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

### PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

	STATUS (Check one)				
U.S. APPLICATION N	UMBER U	J.S. FILING DATE	PATENTED	PENDING	ABANDONED
08/422,280 Ap		April 14, 1995			X
PCT APPLI	 CATIONS DESIGNATIN	G THE U.S.			
PCT APPLICATION NO.	PCT FILING DATE	U.S.FILING NUMBERS			
		ASSIGNED (if any)			
PCT/US96/05009	April 11, 1996			X	

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (List name and registration number)

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Signature of Inventor 201.  1 Ignatus Britto.	Signature of Inventor 202	Signature of Inventor 203
1 Ignotus Britto. Date 7th, Jan, 1999	Date .	Date ,
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Date	Date	Date
Signature of Inventor 207	Signature of Inventor 208	Signature of Inventor 209
Date	Date	Date
Signature of Inventor 210		
Date	7	

		INED DECLARATION Reference to PCT International		APPLICATION AND	POWER OF ATTORNEY	ATTORNEY'S DOCKET NUMBER GI2180USW				
I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:  METERED DOSE INHALER FOR BECLOMETHASONE DIPROPIONATE  the specification of which (check only one item below):  [ ] is attached hereto with Preliminary Amendment.  [X] was filed as United States application Serial No08/945,141on14 October 1997 and was amended on(if applicable).  [X] was filed as PCT international application Number _PCT/US96/05009on11 April 1996		As below named	d inventor. I here	by declare that:						
(if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:    METERED DOSE INHALER FOR BECLOMETHASONE DIPROPIONATE		My residence, post office	e address and citiz	zenship are as stated bel	ow next to my name.					
the specification of which (check only one item below):  [ ] Jis attached hereto with Preliminary Amendment.  [X] was filed as United States application Serial No. 08/945,141 on 14 October 1997 and was amended on (if applicable).  [X] was filed as PCT international application Number PCT/US96/05009 on 11 April 1996  and was amended under PCT Article 19 on (if applicable).  [ I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above.  [ I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 and all information which became available between the filing of the prior application and the nationa or PCT international filing date of the continuation-in-part application.  [ I hereby claim foreign priority benefits under Title 35, United States Code. § 119 (a)-(d) or §365(b) of any foreign applications(s) for patent or inventor's certificate or 365(a) of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified before that of the application(s) on which priority is claimed:  [ PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:		(if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention								
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the Paten	t and Trademark Office	ce connected therewith. (I	ist name and reg	istration number)	d/or agent(s) to prose	cute this application a	nd transact all business in
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= ::	oert H. Brink	Reg. No. 36,094		Shah R. Makujina	Reg. No. 41,174		
Send C	orrespondence to:					Direct Telephone Ca	ills to:
å: ≟::	David J. Levy, Pate Global Intellectual	Property Department				Gerald M	I. Murphy, Jr.
	Glaxo Wellcome Ir	ıc.					205-8000
	Five Moore Drive,						
ge n	Research Triangle FULL NAME	Park, NC 27709 FAMILY NAME		FIRST GIVEN NAME		0.000	
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1	POST OFFICE ADDRESS	Glaxo Wellcome I	ne.	RTP	•	NC 27709, US	DUNTRY
	11001400	Five Moore Drive, P				RC 27709, US	
2	FULL NAME OF INVENTOR	FAMILY NAME HERMAN		FIRST GIVEN NAME Craig		SECOND GIVEN NAME Steven	/INITIAL
	RESIDENCE &	CITY		STATE OR FOREIGN C	OUNTRY	COUNTRY OF CITIZEN	SHIP
0	CITIZENSHIP POST OFFICE	Raleigh POST OFFICE ADDRESS		NC CITY		US STATE & ZIP CODE/CO	WINDOW .
2	ADDRESS	Glaxo Wellcome I		RTP		NC 27709, US	UNIKI
	FULL NAME	Five Moore Drive, P	O Box 13398	FIRST GIVEN NAME			
2 .	OF INVENTOR	LI-BOVET		Li		SECOND GIVEN NAME	/INITIAL
0	RESIDENCE & CITIZENSHIP	Scotch Plains		STATE OR FOREIGN C	OUNTRY	COUNTRY OF CITIZEN	SHIP
	POST OFFICE	POST OFFICE ADDRESS		CITY		STATE & ZIP CODE/CO	UNTRY
3	ADDRESS	172 Spruce Mill Lan	e	Scotch Plains		NJ 07076, US	
2	FULL NAME OF INVENTOR	FAMILY NAME RIEBE		first given name Michael		SECOND GIVEN NAME Thomas	/INITIAL
0	RESIDENCE & CITIZENSHIP	CITY Raleigh		STATE OR FOREIGN C	OUNTRY	COUNTRY OF CITIZEN	SHIP
4	POST OFFICE	POST OFFICE ADDRESS		CITY		STATE & ZIP CODE/CO	UNTRY
	ADDRESS	Glaxo Wellcome In Five Moore Drive, P		RTP		NC 27709, US	
2 .	FULL NAME OF INVENTOR	FAMILY NAME		FIRST GIVEN NAME		SECOND GIVEN NAME	INITIAL
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2	INVENTOR					3_03112 G11	
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. to PCT International	Applications)			GI2180USW
As below named	d inventor. I hereb	by declare that:		
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			e is listed below) or an original, fin imed and for which a patent is sou	
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	t and Trademark Office					= 22 =Banda) to broad	and application o		
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Send C	orrespondence to:				······································		Direct Telephone C	alls to:	
5	David J. Levy, Pat	ent Counsel					C143	6 3 6 to	
<u> </u>	Global Intellectual Glaxo Wellcome In		tment				Gerald M. Murphy, Jr. (703) 205-8000		
3	Five Moore Drive,						(,,,,	, 200 0000	
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79 <sub>1</sub> d	FULL NAME	FAMILY NAME			FIRST GIVEN NAME		SECOND GIVEN NAMI	E/INITIAL	
2	OF INVENTOR	ASHURST			Ian STATE OR FOREIGN COUNTRY		Car;	NSHIP	
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i	ADDRESS	Glaxo Well		12200	RTP		NC 27709, US		
	ELII I MANGE	Five Moore I	Drive, PO Bo	X 13398	FIRST GIVEN NAME		SECOND GIVEN NAM	EUNITIAI	
2	FULL NAME OF INVENTOR	HERMAN			Craig		Steven	E/HVII IAL	
_	RESIDENCE &	CITY			STATE OR FOREIGN	COUNTRY	COUNTRY OF CITIZE	NSHIP	
0	CITIZENSHIP	Raleigh			NC	·	US		
١,	POST OFFICE	Glaxo Well			RTP		NC 27709, US	OUNTRY	
2	ADDRESS	Five Moore Drive, PO Box 133		x 13398			1102,00		
<b></b>	FULL NAME	FAMILY NAME			FIRST GIVEN NAME	· · · · · · · · · · · · · · · · · · ·	SECOND GIVEN NAM	E/INITIAL	
2	OF INVENTOR	LI-BOVET	· · · · · · · · · · · · · · · · · · ·		Li				
0	RESIDENCE &	Scotch Plains			STATE OR FOREIGN COUNTRY  NJ		COUNTRY OF CITIZENSHIP CH		
	POST OFFICE	1			CITY			OUNTRY	
3	ADDRESS	172 Spruce I			Scotch Plains		NJ 07076, US		
2	FULL NAME	FAMILY NAME RIEBE			FIRST GIVEN NAME		SECOND GIVEN NAM Thomas	E/INITIAL	
0	OF INVENTOR RESIDENCE &	CITY		Michael STATE OR FOREIGN CO		COUNTRY	COUNTRY OF CITIZE	ENSHIP	
*	CITIZENSHIP	Raleigh			NC		US		
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COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (Continued - Includes References to PCT International Applications)							
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2	FULL NAME OF INVENTOR	FAMILI NAME		THE CIVENICAL	02001		
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6	ADDRESS	1031 OFFICE ADDRESS					
	FULL NAME OF	FAMILY NAME		FIRST GIVEN NAME	SECO	ND GIVEN NAME/INITIAL	
2	INVENTOR RESIDENCE &	CITY		STATE OR FOREIGN COUNTRY	COUN	TRY OF CITIZENSHIP	
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# Supplemental Declaration COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY

	Reference to PCT International		HITEICATION AND I	OWER OF ATTORNET	DOCKET NUMBER GI2180USW					
	As below name	ed inventor. I here	eby declare that:							
	My residence, post office address and citizenship are as stated below next to my name.									
	I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:									
	ME	TERED DOSE IN	NHALER FOR BECLO	METHASONE DIPROPIONA	TE					
	the specification of which	ch (check only one	e item below):							
	[ ]is attached hereto wi	th Preliminary An	nendment.							
		l States application plicable).	n Serial No. <u>08/945,14</u>	1 on 14 October 1997 and	was amended on					
	[X] was filed as PCT in	ternational applic	ation Number <u>PCT/US</u>	06/05009 on 11 April 1996						
	and was amended t	ınder PCT Article	nder PCT Article 19 on(if applicable).							
der trait des sein des traits des	I hereby state that I have as amended by any ame	e reviewed and un ndment specifical	derstand the contents of ly referred to above.	the above-identified specification	a, including the claims,					
U.S.	I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 and all information which became available between the filing of the prior application and the national or PCT international filing date of the continuation-in-part application.									
the state of the s	I hereby claim foreign priority benefits under Title 35, United States Code. §119 (a)-(d) or §365(b) of any foreign applications(s) for patent or inventor's certificate or 365(a) of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) having a filing date before that of the application(s) on which priority is claimed:									
PRIOR				LAIMS UNDER 35 U.S.C. 119:						
(if	COUNTRY PCT indicate PCT)	APPLICA	TION NUMBER DATE OF FILE (day, month, ye		PRIORITY CLAIMED UNDER 35 USC 119					
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5.	· · · · · · · · · · · · · · · · · · ·									
hereby	claim the benefit under	Title 35, United S	tates Code §119(e) of an	y United States provisional appli	cation(s) listed below:					
	Application No.	•	Filing Date	(MM/DD/YYYY)						
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COMB	INED DECLAR	ATION FOR	PATENT A	PDI ICA	ATION AND DOL	WED OF	ATTORNEY'S D	OCKET NUMBER
COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (Continued - Includes References to PCT International Applications)							GI2180USW	
	designating the Unit in that/those prior ap	ted States of Amer oplication(s) in the n as defined in Tit	rica that is/are l manner provid le 37, Code of I	isted below led by the t rederal Reg	or and, insofar as the suffirst paragraph of Title gulations, §1.56 which	bject matter of each of 35, United States Co	of the claims of this ap	ternational application(s) plication is not disclosed dge the duty to disclose of the prior application(s)
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				oint the fo	llowing attorney(s) and	d/or agent(s) to prose	cute this application a	nd transact all business in
the Paten	t and Trademark Offic	ce connected there	with. (List nan	ne and regi	stration number)		appirounou u	are duribuot un oubinous a
David J. Levy Reg. No. 27,655 Charles E. Dadswell Reg. No. 35,851 Karen L. Prus Reg. No. 39,337 Robert H. Brink Reg. No. 36,094				James P. Riek Robert T. Hrubiec Frank P.Grassler Shah R. Makujina	Reg. No. 39,009 Reg. No. 36,392 Reg. No. 31,164 Reg. No. 41,174	Gerald M. Murphy, Jr. Reg. No. 28,977		
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Marine Mr.	orrespondence to: David J. Levy, Pat						Direct Telephone Ca	ilis to:
u Di	Global Intellectual	Property Depart	ment					I. Murphy, Jr.
	Glaxo Wellcome In Five Moore Drive,						(703)	205-8000
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